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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/074,220	02/12/2002	Tadashi Kumamoto	UTSD:771US	6187

7590 12/27/2004

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EXAMINER	
SAKELARIS, SALLY A	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 12/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/074,220	KUMAMOTO ET AL.	
	Examiner	Art Unit	
	Sally A Sakelaris	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 14-17* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/2002 & 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-12 and 14-17 without traverse is acknowledged in their response submitted 10/04/2004.

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged. The present application's claim to benefit of a U.S. provisional Application 60/273,212 filed March 1, 2001, is granted.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 4/8/2003 and 4/29/2003 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The listing of references in the specification(pages 78-99) is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

The disclosure is objected to because of the following informalities: The specification appears to include misnumbered experiments. Pages 68-73 include content referring to Example 1, while on page 74 applicant's description shifts to Example 3. There is no Example 2 present.

It is believed that no content is missing as all page numbers are accounted for, however the Example 3 appears to represent Example 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1-12 and 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of predicting irritant potential of a candidate substance comprising: providing a keratinocyte cell that releases ATP or ADP in response to an inflammatory agent, culturing said cell with a candidate substance; and determining ATP or ADP release from said keratinocyte cell wherein an increase as compared to ATP and ADP release in the absence of said candidate substance, indicates that said candidate substance is an irritant, but does not reasonably provide enablement for the same method practiced with all cell types and the measurement of all types of released nucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman.

They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-12 and 14-17 are broadly drawn to methods of predicting irritant potential of a candidate substance in all cell types exposed to said irritant through the detection of the release of all types of nucleotides in comparison to cells not exposed to said irritant. In fact, the specification recites that the present invention illustrates a nucleotide-mediated pathogenic mechanism and a CD39-dependent protective mechanism for the development of irritant contact dermatitis. However, as will be further discussed, there is no support in the specification and prior art for the method of predicting irritant potential of a candidate substance in all cell types exposed to said irritant through the detection of the release of all types of nucleotides in comparison to cells not exposed to said irritant, only for the method wherein the release of ATP and ADP from keratinocytes is practiced. The invention is an class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The specification recites that in keratinocytes released ATP and ADP after exposure to CO, BAC and EPP(Pg. 73 line 20). The authors' post date filing art(Mizumoto et al. Journal of Invest. Dermat. Vol. 121, No. 5, 11/2003 pgs. 1066-1072) teaches that ATP release from keratinocytes correlated with the administration of "a vast majority 19/20 of the tested compounds" including corrosive and non-corrosive chemicals that are structurally diverse(Pg. 1070 rt side). The specification and art also teach that it is only the release of ATP and ADP(Pg.

73) that occurs following the treatment with one of the above, taught candidate substances. Furthermore, the specification and prior art teach only that in keratinocytes cells is the above method able to be practiced. There is no evidence that said above method would be operable in any cell type other than keratinocytes and with the detection of release of any nucleotide other than ATP and ADP. In example 1 of the specification, Pam 212 keratinocytes released ATP and ADP rapidly after exposure to CO, BAC or EPP while CD39-/- mice exhibited exacerbated irritant contact dermatitis to the same chemicals and locally administered apyrase reduced the extent of acute inflammatory responses in CD39-/- mice. However, there is no correlation between the release of any nucleotide besides ATP and ADP from any cell other than a keratinocyte.

There is a great deal of unpredictability in the practicing of this method in every possible cell type. Alberts et al.(1998 www.essentialcellbiology.com) teach that there are over 200 types of cells in the human body, assembled into a variety of types of tissue such as epithelia, connective tissue, muscle, nervous tissue, blood, germ, and sensory cells including a myriad of different cell types such as keratinocytes, fibroblasts, glial cells, cardiac muscle cells, erythrocytes, sperm, and rod cells just as an example. Most tissues contain even a further mixture of cell types. There is a high level of unpredictability associated with practicing the claimed method in such a varied cell population, each cell consisting of a radically different composition. Furthermore, as applicants include the specific embodiment of their invention in fibroblasts without any teachings of their method being practiced in such a cell type, it should be noted that fibroblasts and keratinocytes are different cell types, even more so than just belonging to different connective tissues sub-group and epithelia tissue sub-group respectively. Offord et al.(Carcinogenesis Vol. 14 no. 12 pp.2447-2455, 1993) teach the occurrence of "different stability of AP1 proteins in human keratinocyte and fibroblast cells"(title). Offord et al. teaches that the "quantitative difference in AP1 proteins between human keratinocytes and fibroblasts is

due to a difference in protein stability" which is in turn due to varying Jun and Fos stability, varying nuclear extract composition, etc. As a result, it is highly unpredictable to practice the method for predicting irritant response in a completely different cell type than what is taught in the specification since the art has specifically asserted fibroblasts and keratinocytes to have non-redundant characteristics and compositions.

The art also teaches much unpredictability involved in using all nucleotides interchangeably, specifically since each nucleotide has a different function in a cell. While a nucleotide consists of a nitrogen-containing base, a 5-carbon sugar, and one or more phosphate groups, they each have different functions and physical properties depending on for instance the base(A, G, T, C, or U) with which they are associated, the molecule to which they are potentially conjugated i.e. allowing to carry chemical energy in the form of ATP, combining with other groups to form enzymes as is the case with conenzyme A(CoA) or as specific signaling molecules such as cyclic AMP(cAMP). The ATP molecule serves as the energy currency of the cell, CTP functions for example through binding to regulatory dimmers converting aspartate transcarbamoylase to its inactive T state(Alberts et al. Molecular biology of the Cell, 3rd edition 1994 page 200), hydrolysis of GTP occurs in microtubule polymerization, etc. Each nucleotide has different uses and is therefore highly unpredictable to prophesize that release of each and every one would correlate in the same was as that which is observed for ATP and ADP in the specification.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to apply this technology to all cell types, and all nucleotides. For any cell type, one must also consider (a) the ability of any cell and its characteristic components to respond in the same way as that of the contemplated keratinocytes;

and (b) the predictable release of all types of nucleotides from all types of cells. For example, with regard to the cell type issue, while keratinocytes are relatively similar among different species, all cell types are not as asserted above, the time table necessary to achieve efficacious detection of a presently prophetic relationship to all cell types and their release of all nucleotides would require a very large quantity of experimentation for *in vitro* and *in vivo* applications. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Working Examples

The specification has no working examples of the method for predicting irritant potential using any cell's release of any nucleotide.

Guidance in the Specification.

The specification provides no evidence that the un-disclosed, various cell types(fibroblasts etc) would predictably correlate in the same manner as do the studied and contemplated keratinocytes with the prophetic release of any nucleotide other than the asserted ATP and ADP molecules. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the association between nucleotide release and irritant potential of a candidate substance is highly unpredictable among all cell types the factor of unpredictability weighs heavily in favor of undue experimentation. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized problems in the use of the different cell types as presently, broadly claimed (i.e encompassing a method in any cell with the release of any nucleotide). Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sally A Sakelaris whose telephone number is 571-272-0748. The examiner can normally be reached on M-Fri, 9-6:30 1st Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on 571-272-0745. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sally Sakelaris

12/22/2004

JEFFREY FREDMAN
PRIMARY EXAMINER
12/21/04